

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problems Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|--|--|--|--|
| (51) International Patent Classification ⁷ : A61K 9/70, 31/465 | | A1 | (11) International Publication Number: WO 00/37058 (43) International Publication Date: 29 June 2000 (29.06.00) |
| (21) International Application Number: PCT/US99/29731 (22) International Filing Date: 14 December 1999 (14.12.99) | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). | |
| (30) Priority Data: 60/112,730 18 December 1998 (18.12.98) US 60/124,679 16 March 1999 (16.03.99) US 60/126,798 30 March 1999 (30.03.99) US | | Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> | |
| (71) Applicant: ALZA CORPORATION [US/US]; 1900 Charleston Road, P.O. Box 7210, Mountain View, CA 94039-7210 (US). | | | |
| (72) Inventor: GALE, Robert, M.; 1276 Russell Avenue, Los Altos, CA 94024 (US). | | | |
| (74) Agents: STONE, Steven, F. et al.; Alza Corporation, 1900 Charleston Road, P.O. Box 7210, Mountain View, CA 94039-7210 (US). | | | |
| (54) Title: TRANSPARENT TRANSDERMAL NICOTINE DELIVERY DEVICES | | | |
| (57) Abstract A transparent transdermal delivery device for delivering nicotine which has an Opacity Index of less than 48.6 %. | | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|---------------------------------------|----|---|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakhstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LJ | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |

TRANSPARENT TRANSDERMAL NICOTINE DELIVERY DEVICESClaim of Priority

5

The inventor claims the benefit of the filing date of provisional applications S.N. 60/112,730; 60/124,679 and 60/126,798.

Field of the Invention

10

The present invention relates to transdermal delivery devices for administering nicotine for use in smoking cessation treatments. In particular, the invention is directed to transdermal nicotine delivery devices which are transparent.

15

Background of the Invention

The transdermal route of parenteral drug delivery provides many advantages over other administration routes. Transdermal systems for delivering a wide variety of drugs or other beneficial agents are described in U.S. Patent Nos. 3,598,122; 3,598,123; 3,731,683; 3,797,494; 4,031,894; 4,144,317; 4,201,211; 4,286,592; 4,314,557; 4,379,454; 4,435,180; 4,559,222; 4,568,343; 4,573,995; 4,588,580; 4,645,502; 4,698,062; 4,704,282; 4,725,272; 4,781,924; 4,788,062; 4,816,258; 4,849,226; 4,904,475; 4,908,027; 4,917,895; 4,938,759; 4,943,435; 5,004,610; 5,071,656; 5,122,382; 5,141,750; 5,284,660; 5,314,694; 5,342,623; 5,411,740; and 5,635,203, which are hereby incorporated in their entirety by reference.

The administration of nicotine buccally, nasally and transdermally to assist a patient desiring to quit smoking has been shown to be clinically effective in reducing the rate of recidivism. Nicotine chewing gum and

transdermal nicotine are two of the most widely used forms of nicotine replacement therapy currently available. Transdermal devices for administering nicotine are disclosed in U.S. Patent Nos. 4,597,961; 4,758,434; 4,764,382; 4,839,174; 4,908,213; 4,915,950; 4,943,435; 5 4,946,853; 5,004,610; 5,016,652; 5,077,104; 5,230,896; 5,411,739; 5,462,745; 5,508,038; 5,599,554; 5,603,947 and 5,726,190, for example, which are hereby incorporated in their entirety by reference.

Most of the transdermal drug delivery devices of the prior art utilize an impermeable backing on the skin distal surface of the device to protect the 10 device from damage and to prevent loss of the active ingredient(s). In order to improve user satisfaction, these backing layers are often tinted to a color similar to skin tones. However, as can be readily appreciated, it is not commercially practical to provide pigmented backing layers for transdermal systems which approximate all skin colors.

15 Another approach that has been taken is to provide transparent transdermal systems in which all elements forming a device are sufficiently transparent to permit the natural skin color to be visible through the device. Marketed products which take this approach include the Alora® and Climara® estrogen replacement patches and the Duragesic® transdermal fentanyl 20 delivery system. When these devices are applied to the skin, the patient's natural skin color is visible through the patch, making the presence of the patch extremely inconspicuous. Government regulations require that these products bear identifying indicia, but the indicia can be printed on these 25 devices in light colored or white ink which is not noticeable from a distance of several feet, but is still readable on close inspection.

Such transparent patches have been found useful with non-volatile drugs such as fentanyl and hormone replacement steroids, but no such transparent product has been developed for the delivery of nicotine.

Nicotine is a liquid alkaloid that is colorless, volatile, strongly alkaline, 30 readily oxidized, subject to degradation on exposure to light and highly

permeable through not only the human skin, but also many of the polymers conventionally used in the fabrication of backing layers and packaging materials for transdermal products (see for example U.S. Patent 5,077,104).

As a result, the backing layers of the transdermal nicotine delivery devices

- 5 currently available utilize opaque, skin-colored multilaminate films which typically contain a metallized layer, such as aluminum.

Not only do the commercially available transdermal nicotine patches use opaque backings, but many of these devices, due to the complexities of handling and processing nicotine, have other components which are not

- 10 transparent. For example, the original Prostep® transdermal nicotine product used a drug reservoir in the form of an opaque white gel, held in place by an opaque adhesive overlay. The Habitrol® and Nicotrol® nicotine patches incorporated absorbant pads in the drug reservoir in which the nicotine was absorbed.

- 15 It has also been proposed to co-administer nicotine with other substances that improve nicotine cessation therapy. See, for example, patents 4,908,213; 5,599,554; and 5,726,190 noted above, and WO 97/33581.

20

SUMMARY OF THE INVENTION

The present invention relates to transparent transdermal delivery devices for the transdermal administration of nicotine, either alone or in combination with other agents.

- 25 Such devices should be sufficiently transparent so that the subject's skin can be clearly visible through the device when it is placed on the skin. Identifying indicia can be printed on the device in light colored or white ink in a manner which is not noticeable from a short distance, but is readable on close inspection.

30

DETAILED DESCRIPTION OF THE INVENTION

Preferred devices of this invention utilize, as the backing layer, a

5 transparent polymeric film which has a permeability to nicotine of less than 1
μg / cm² · hr, preferably less than 0.5 μg / cm² · hr, a solubility for nicotine that
is less than 1% by weight and preferably less than 0.1 %. Such films are
preferably less than about 6 mils thick and most preferably about 2-4 mils
thick. Such films are used in combination with one or more of the conventional
10 elements of a transdermal device (other than the removable release liner)
such as the drug reservoir, adhesive and rate controlling membranes, which
must also be sufficiently transparent as to permit the natural skin color to be
clearly visible through the assembled device after placement on the skin. The
finished product should have an Opacity Index of less than about 48.6%,
15 preferably less than about 35.11% and more preferably less than 20%.

In addition to being transparent and being sufficiently impermeable to
nicotine, the backing layer must also have sufficient mechanical strength and
physical integrity to maintain the system intact throughout its intended
administration period, which is typically 18-24 hours, and must provide a
20 stable interface with adjoining layers such as the drug reservoir or adhesive
layers of the transdermal device. This combination of properties is not always
found in one material, and thus the transparent backing layers used on the
devices of this invention can be multilaminate films. In addition to having a low
permeability to nicotine, a backing layer must also have a low solubility for
25 nicotine. This is because nicotine is toxic and it could be dangerous for a
child, for example, to lick the backing layer if it contained a substantial amount
of dissolved nicotine.

Suitable polymer materials possessing properties required by this
invention include Scotchpak® 1220 which is a polyethylene terephthalate
30 /ethylene vinyl acetate (PET EVA), bilaminate film sold by the 3M Company,
Minneapolis, Minnesota, and Saranex® 2057 which is a high density

Polyethylene (HDPE)/ethylene acrylic acid (EAA)/nylon/EAA multilaminate available from the Dow Chemical Company, Midland, Michigan. Nitrile rubber graft copolymers with acrylonitrile and methyl acrylate sold as Barex® films described in U.S. Patent 5,077,104 noted above, can also be used.

5 These films, comprising a graft copolymer formed from about 73-77% acrylonitrile and from about 23-27% methyl acrylate copolymerized in the presence of about 8-10 parts by weight of butadiene/acrylonitrile copolymers containing approximately 70% by weight of polymer units derived from butadiene are preferred backing materials.

10 The transparent transdermal delivery devices of this invention can be of any of the forms described in the aforementioned patents. The preferred form, however, comprises a laminate of the backing layer, a nicotine reservoir layer which contains nicotine dissolved in a carrier at a concentration below the saturation concentration of nicotine in the carrier. If the drug reservoir 15 component is self adhesive, a simple monolithic device could be employed. However, in many cases it is desirable to include additional components such as rate controlling membranes, and a separate adhesive layer for maintaining the devices on the skin such as is described in U.S. Patents 5,004,610 and 5,342,623 listed above. It is further contemplated that in addition to nicotine, 20 the device may also contain other drugs or other active substances which cooperate with or enhance the effect of nicotine in smoking cessation, smoking replacement or smoking substitution therapy. For all these devices, a removable release liner would normally be applied on the adhesive surface of the patch that is used to keep the device on the skin, which release liner is 25 removed prior to use.

Various materials suited for fabrication of the various components are known in the art and are disclosed in the aforementioned patents.

The adhesive component is preferably a pressure sensitive adhesive including, but not limited to, polysiloxanes, polyacrylates, polyurethanes, 30 acrylic adhesives including cross linked or uncross linked acrylic copolymers, vinyl acetate adhesives, ethylene vinylacetate copolymers, and natural or

synthetic rubbers including polybutadienes, polyisoprenes, and polyisobutylene adhesives, and mixtures and graft copolymers thereof. The devices may also be provided with hydrophilic water absorbing polymers known in the art such as polyvinyl alcohol and polyvinyl pyrrolidone individually or in combination. The adhesive can be used to form a monolithic delivery device in which the nicotine is dissolved in the adhesive to form a self-adhesive drug reservoir. Alternatively, the adhesive can be applied to the surface of a non-adhesive reservoir in which nicotine is dissolved, to form a multilaminate device. A rate-controlled membrane can also be interfaced between the nicotine reservoir and the adhesive, as is known to the art.

The nicotine can be administered in combination with another agent which could include anti-anxiolytics, antihypertensives, antidepressants, and appetite suppressants, such as fluoxetine, caffeine, buspirone, phenylpropanolamine, clonidine, paroxetine, citalopram, and sertraline.

The nicotine in the device is present in the reservoir at a subsaturated condition (i.e. less than unit activity) such that no undissolved nicotine is present in the reservoir. If other agents are present in the device, they are preferably present fully dissolved, but can be present in undissolved form so long as the end product displays the proper degree of transparency.

In the present invention, nicotine and optionally other agents to be co-administered are delivered through the skin or other body surface at a therapeutically effective rate for a predetermined time period which for nicotine is preferably 16-24 hours.

The transdermal therapeutic devices of the present invention are prepared in a manner known in the art, such as by those procedures described in the transdermal device patents listed previously herein.

The following example is offered to illustrate the practice of the present invention and is not intended to limit the invention in any manner.

EXAMPLE 1

Various commercially available transdermal patches were tested to determine their transparency and compared to the transparent nicotine patches according to this invention. The nicotine patches were prepared as set forth in Example IV of U.S. Patent No. 5,004,610 with a PET/EVA (Scotchpak® 1220, 3M, Minneapolis, MN) or Saranex® (Dow Chemical Company, Midland, MI) backing substituted for the Scotchpak 1006 backing. The light transmitted through the various systems was measured by a Macbeth 1500/Plus color measurement system (Kollmorgen Instruments Corp., Newburgh, NY). Table 1 shows the Opacity Index, which is the percentage of incidental light which is absorbed by passage through the device, for the various systems tested.

15

Table 1: Patch Opacity

| Patch | Opacity Index |
|--|---------------|
| Minitran® | 48.6% |
| Alora® | 20.21% |
| FemPatch® | 35.11% |
| Climara® | 19.33% |
| Ex. 1 - Nicotine with Saranex® backing | 17.04% |
| Ex. 1 - Nicotine with PET/EVA backing | 19.66% |

The Minitran® nitroglycerine system is clearly visible from a distance of about 5 feet, whereas the FemPatch® is significantly less noticeable. The Alora®, Climara® and Nicoderm® patches, however, are extremely inconspicuous. Accordingly, transdermal devices according to this invention should have an Opacity Index less than 48.6%, preferably less than 35.11%, more preferably less than 20%.

Having thus generally described our invention and preferred embodiments thereof, it is apparent that various modifications and substitutions will be apparent to workers skilled in the art. These modifications and substitutions can be made without departing from the scope
5 of our invention which is limited only by the following claims.

We Claim:

1. A device for the transdermal administration of nicotine comprising a
5 backing layer, a drug reservoir layer containing nicotine carried by said
backing layer, and means for maintaining the device in nicotine transmitting
relationship with the skin, wherein the device is sufficiently transparent to
permit the skin of the subject to which it is applied to be visible through said
device.
- 10 2. The device of claim 1 wherein said backing has a nicotine permeability
of less than about 1.0 µg / cm² · hr.
- 15 3. A device according to claim 1 wherein the backing has a nicotine
permeability of less than 0.5 µg / cm² · hr.
4. A device according to claim 2 wherein the backing has a solubility for
nicotine of less than about 1 wt%.
- 20 5. A device according to Claim 3 wherein the backing has a solubility for
nicotine of less than about 0.1 wt%.
6. A device according to claim 4 wherein the device has an Opacity Index
less than about 48.6%.
- 25 7. A device according to claim 6 wherein the device has an Opacity Index
of less than 35.11%.
8. A device according to claim 6 wherein the device has an Opacity Index
30 of less than 20%.

9. The device of claim 1 wherein said backing is formed from a material selected from the group consisting of PET/EVA laminates, HDPE/EAA/nylon/EAA multilaminates and a film comprising a graft copolymer formed from about 73-77% acrylonitrile and from about 23-27% methyl acrylate copolymerized in the presence of about 8-10 parts by weight of butadiene/acrylonitrile copolymers containing approximately 70% by weight of polymer units derived from butadiene.

INTERNATIONAL SEARCH REPORT

| |
|----------------------|
| Int'l Application No |
| PCT/US 99/29731 |

| |
|-------------------------------------|
| A. CLASSIFICATION OF SUBJECT MATTER |
| IPC 7 A61K9/70 A61K31/465 |

According to International Patent Classification (IPC) or to both national classification and IPC

| |
|--------------------|
| B. FIELDS SEARCHED |
|--------------------|

Minimum documentation searched (classification system followed by classification symbols)

| |
|------------|
| IPC 7 A61K |
|------------|

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

| |
|--|
| C. DOCUMENTS CONSIDERED TO BE RELEVANT |
|--|

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | US 5 626 866 A (EBERT CHARLES D ET AL) 6 May 1997 (1997-05-06) abstract column 14; example 6 column 13; example 4 | 1-9 |
| X | US 5 372 819 A (GODEBEY KRISTIN J ET AL) 13 December 1994 (1994-12-13) column 1, line 65 -column 2, line 41 column 5, line 11 - line 16 | 1-8 |
| X | EP 0 563 507 A (MLI ACQUISITION CORP II) 6 October 1993 (1993-10-06) abstract page 5, line 25 - line 30 page 15, line 22 - line 23 page 20, line 9 - line 10 | 1-8 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"8" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

18 April 2000

26/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Muller, S

2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/29731

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-8 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of Invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-8

Present claims 1-8 relate to a device defined by reference to a desirable characteristic, namely the term "sufficiently transparent", the nicotine permeability, the solubility for nicotine, and the Opacity Index. The claims cover all device having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such devices. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the device by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the devices with transparent backings mentioned in examplel in the description at pages 7-8.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

| |
|-----------------------------|
| Inte rial Application No |
| PCT/US 99/29731 |

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|-------------|------------------|
| US 5626866 A | 06-05-1997 | AU | 676430 B | 06-03-1997 |
| | | AU | 1831895 A | 25-09-1995 |
| | | CA | 2183083 A | 14-09-1995 |
| | | CN | 1143314 A | 19-02-1997 |
| | | EP | 0743842 A | 27-11-1996 |
| | | JP | 9509960 T | 07-10-1997 |
| | | WO | 9524172 A | 14-09-1995 |
| | | ZA | 9501247 A | 12-12-1995 |
| US 5372819 A | 13-12-1994 | US | 5264219 A | 23-11-1993 |
| | | DE | 69314650 D | 20-11-1997 |
| | | DE | 69314650 T | 26-03-1998 |
| | | EP | 0654065 A | 24-05-1995 |
| | | JP | 8500139 T | 09-01-1996 |
| | | WO | 9403539 A | 17-02-1994 |
| EP 0563507 A | 06-10-1993 | AT | 166574 T | 15-06-1998 |
| | | BR | 9203172 A | 19-10-1993 |
| | | CA | 2075517 A,C | 02-10-1993 |
| | | DE | 69225695 D | 02-07-1998 |
| | | DE | 69225695 T | 21-01-1999 |
| | | ES | 2118124 T | 16-09-1998 |
| | | JP | 6335532 A | 06-12-1994 |
| | | KR | 9605143 B | 22-04-1996 |
| | | MX | 9206090 A | 01-10-1993 |
| | | US | 5662926 A | 02-09-1997 |
| | | US | 5679373 A | 21-10-1997 |
| | | US | 5676969 A | 14-10-1997 |
| | | US | 6010715 A | 04-01-2000 |